Defining and Advancing IRB Quality & Effectiveness

October 18, 2024
Multicenter Perioperative Outcomes Group
Annual Meeting

Holly Fernandez Lynch, JD, MBE
Associate Professor
Division of Medical Ethics
University of Pennsylvania

Roadmap

- History and purpose of IRBs
- What makes it hard to evaluate IRBs
- Where have we gone wrong?
- IRB reasonableness
- Pillars of IRB Quality

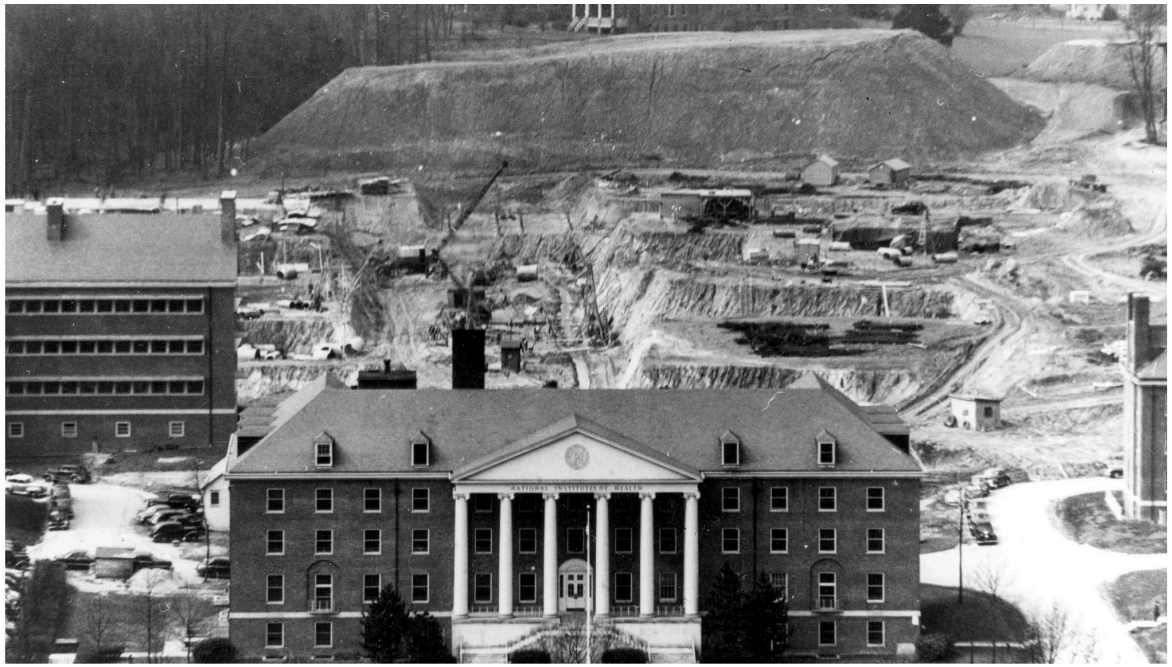
Evidence-Based Medicine v. Evidence-Based Policy

- EBM ideal:
  - Hypothesis → rigorous data collection → implementation of what works + rejection of what doesn't
- Policy-making:
  - Problem/scandal → plausible fix → policy change
  - *Maybe* data collection later
  - *Maybe* policy adjustment later (*sometimes* based on data)
- IRBs: substantial, burdensome policy intervention that has never been subjected to efficacy testing

What Were IRBs Made For?

1950s – NIH Clinical Center Policy

- 1953: NIH Clinical Center opens, with policy on **"Group Consideration of Clinical Research Procedures Deviating from Accepted Medical Practice or Involving Unusual Hazard"**
- Applied to research involving any unestablished, nonstandard, or unusually hazardous procedure
- Investigators proposing such research had to indicate the necessity, basis, and potential hazard for review and approval by committee
- Notion that these decisions shouldn't be left up to any individual – too much inherent COI

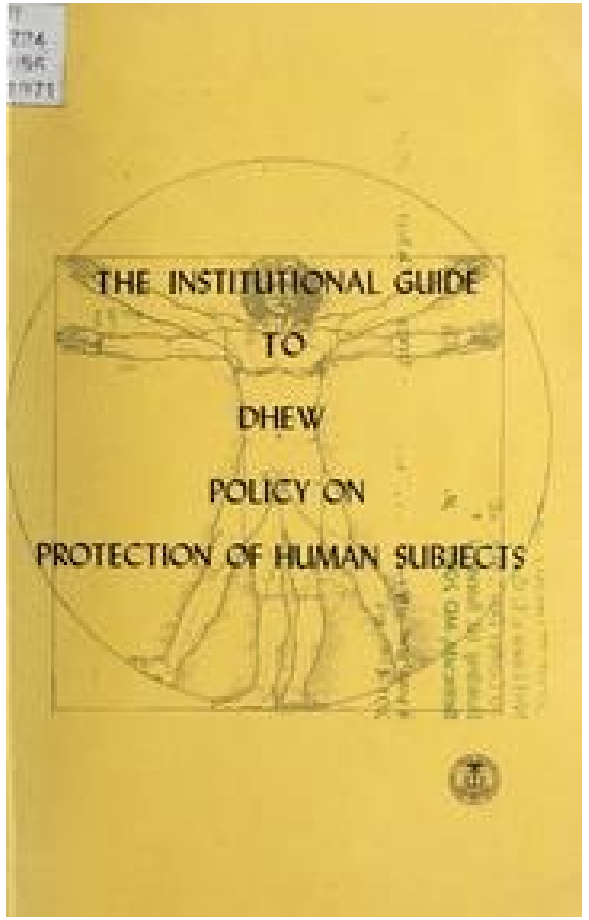


The NIH's clinical research hospital, known as the Clinical Center, 1950. The Clinical Center opened in 1953.
NIH

McCarthy, C., The origins and policies that govern IRBs, Oxford Textbook of Clinical Research Ethics, 2008.

1960s – PHS Policy

- 1960s: more attention to research ethics/examples of concerning studies
- NIH formed **National Advisory Health Council**
  - First concluded NIH should not risk inhibiting research
  - NIH director pushed for NIH to take more responsibility
  - 1966: New NAHC recs adopted for PHS-funded research:
    - Policy requiring awardee institutions to provide local prior review of PI judgment by a committee of "his institutional associates"
    - Determination of rights/welfare, informed consent + risks/benefits
- 1971: Becomes "**Yellow Book**" policy for all of DHEW



McCarthy, C., The origins and policies that govern IRBs, Oxford Textbook of Clinical Research Ethics, 2008.

1970s – Response to PHS Syphilis Study

- 1972: Journalist exposes study at Tuskegee
- 1974: National Research Act
  - "Secretary shall by regulation require" that each awardee for a project involving **biomedical or behavioral** human subjects research submit assurance that it has established an **"Institutional Review Board"** to review its research "in order to **protect the rights of the human subjects of research**"

The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men,

McCarthy, C., The origins and policies that govern IRBs, Oxford Textbook of Clinical Research Ethics, 2008.

Participant Protection

- From an ethical perspective, what do subjects need to be protected from?
  - Risks of investigational interventions
  - Risks beyond those of daily life

- A lot of confusion about what to do with standard of care research
- Very hard for IRBs to be creative and flexible

Beyond Participant Protection

1

Protect participants (+ communities)

2

Promote socially valuable research

3

Foster a culture of ethical concern

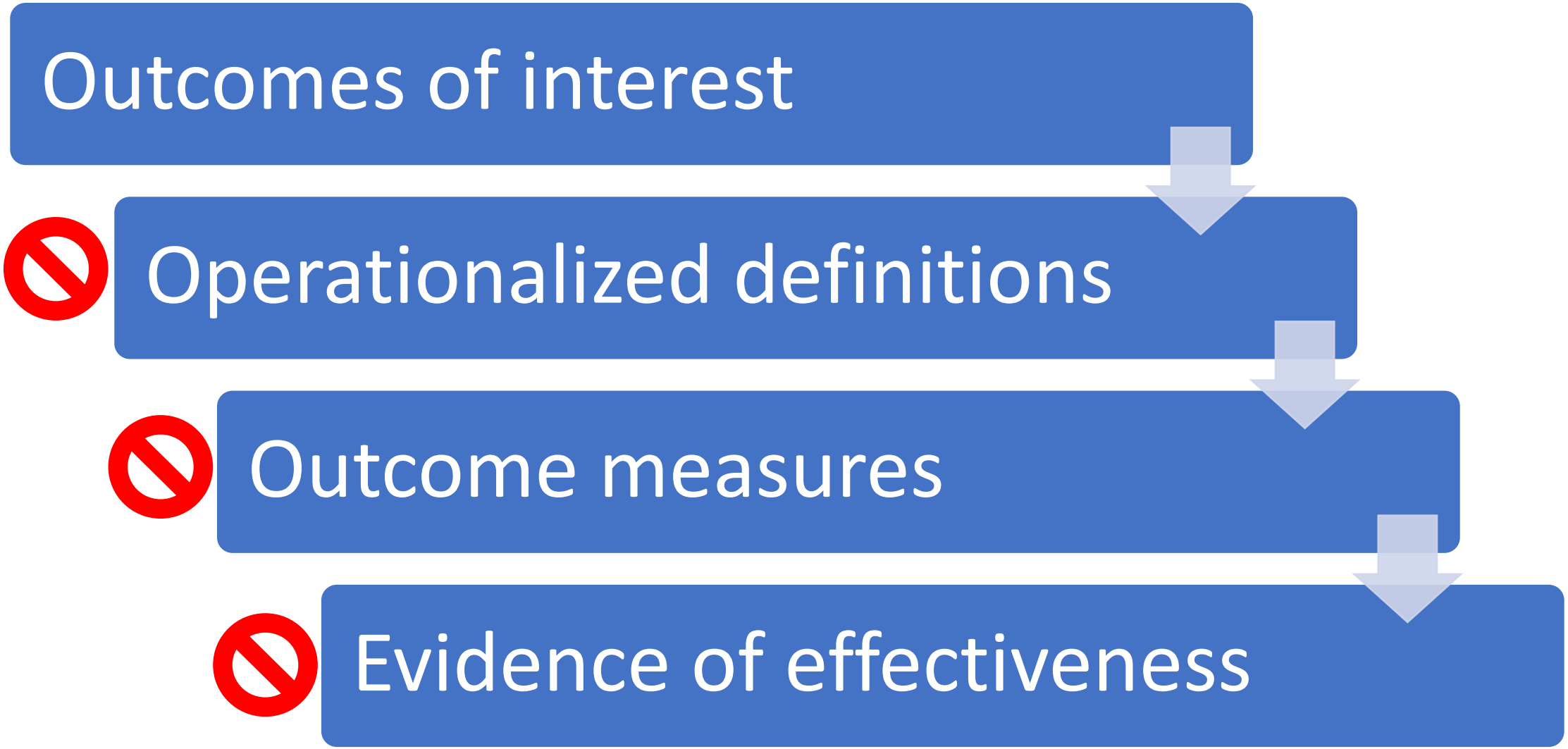
4

Promote public trust in research and the research enterprise

Fernandez Lynch, H, Nicholls S, Meyer MN, Taylor HA. Of parachutes and participant protection: Moving beyond quality to advance effective research ethics oversight. J Emp Res Hum Res Ethics. 2019;14(3):190-96.

Difficulty Operationalizing IRB Quality

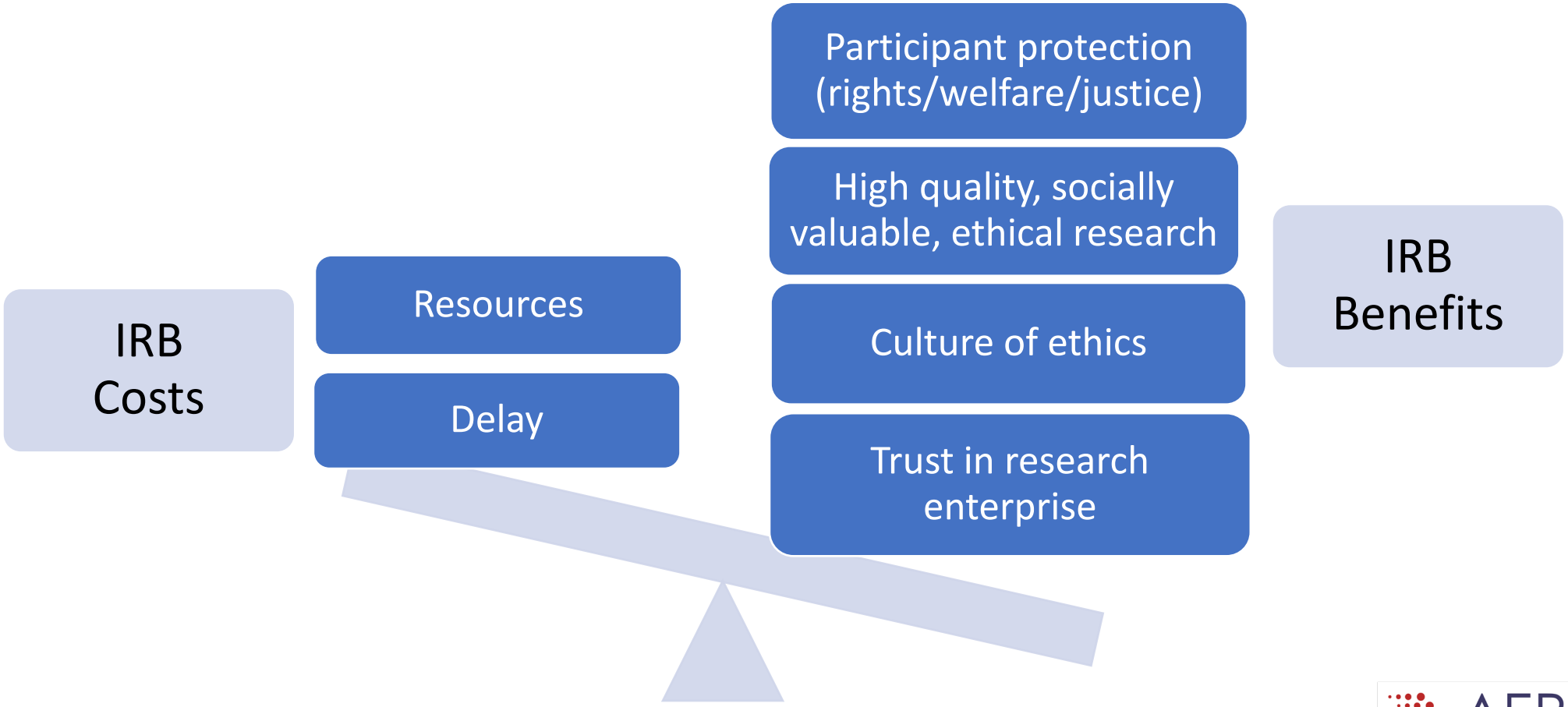
- Desirable IRB outcomes are obvious but they are *subjective* and *amorphous*
- E.g., what exactly does it mean to protect participants?
  - Protect them from AEs → but research is uncertain and has risks
  - Protect them from avoidable AEs → what's avoidable, is it the IRB's fault?
  - Protect them from nonconsensual research → what's sufficient consent?
  - Protect their rights and welfare → do we always agree on how?


Outcomes of interest
Operationalized definitions
Outcome measures
Evidence of effectiveness

Other problems

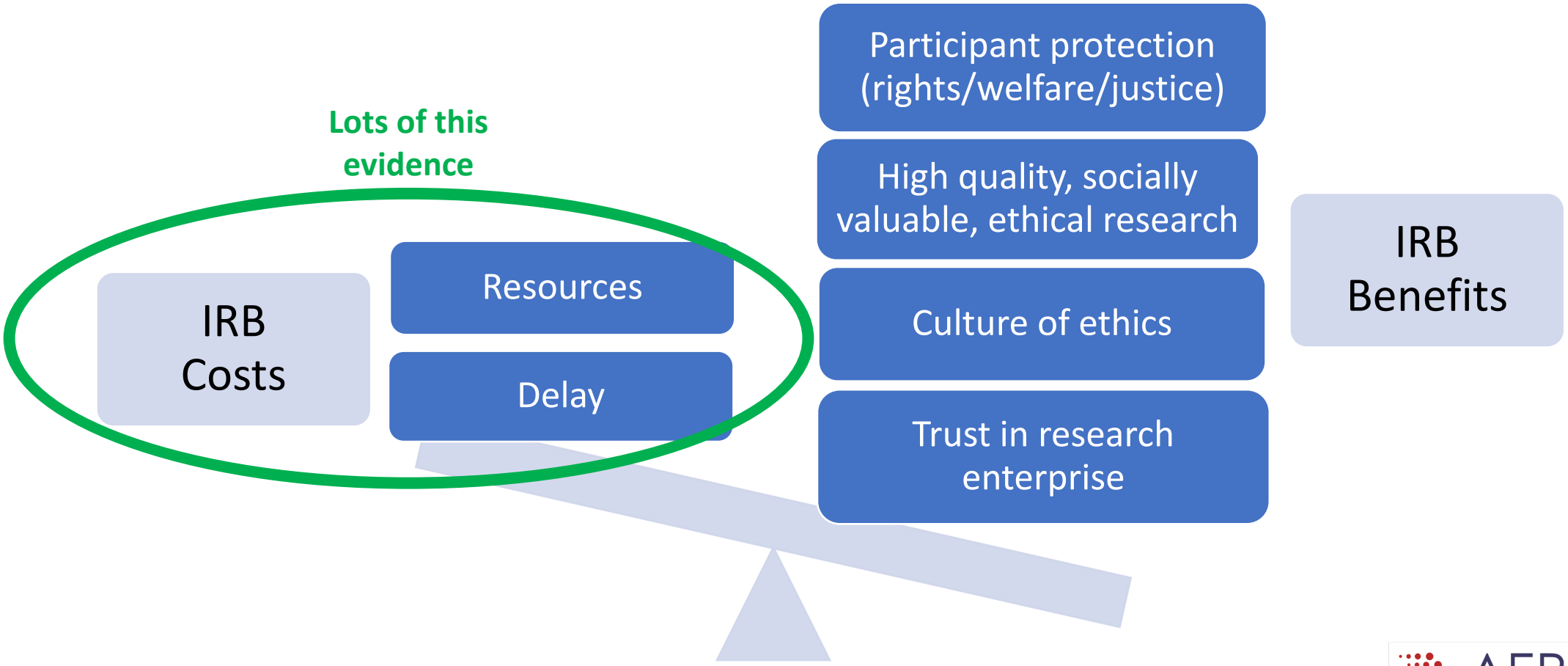
- Easy to measure IRB costs/burdens
- Harder to measure prevention/benefits
- IRBs/HRPPs are only one mechanism of participant protection – lots of confounders
- IRBs can be nontransparent – hard to study
- Not a priority for institutions, regulators, or funders

Underlying Assumptions



AEREO
Advancing Effective Research Ethics Oversight

Underlying Assumptions

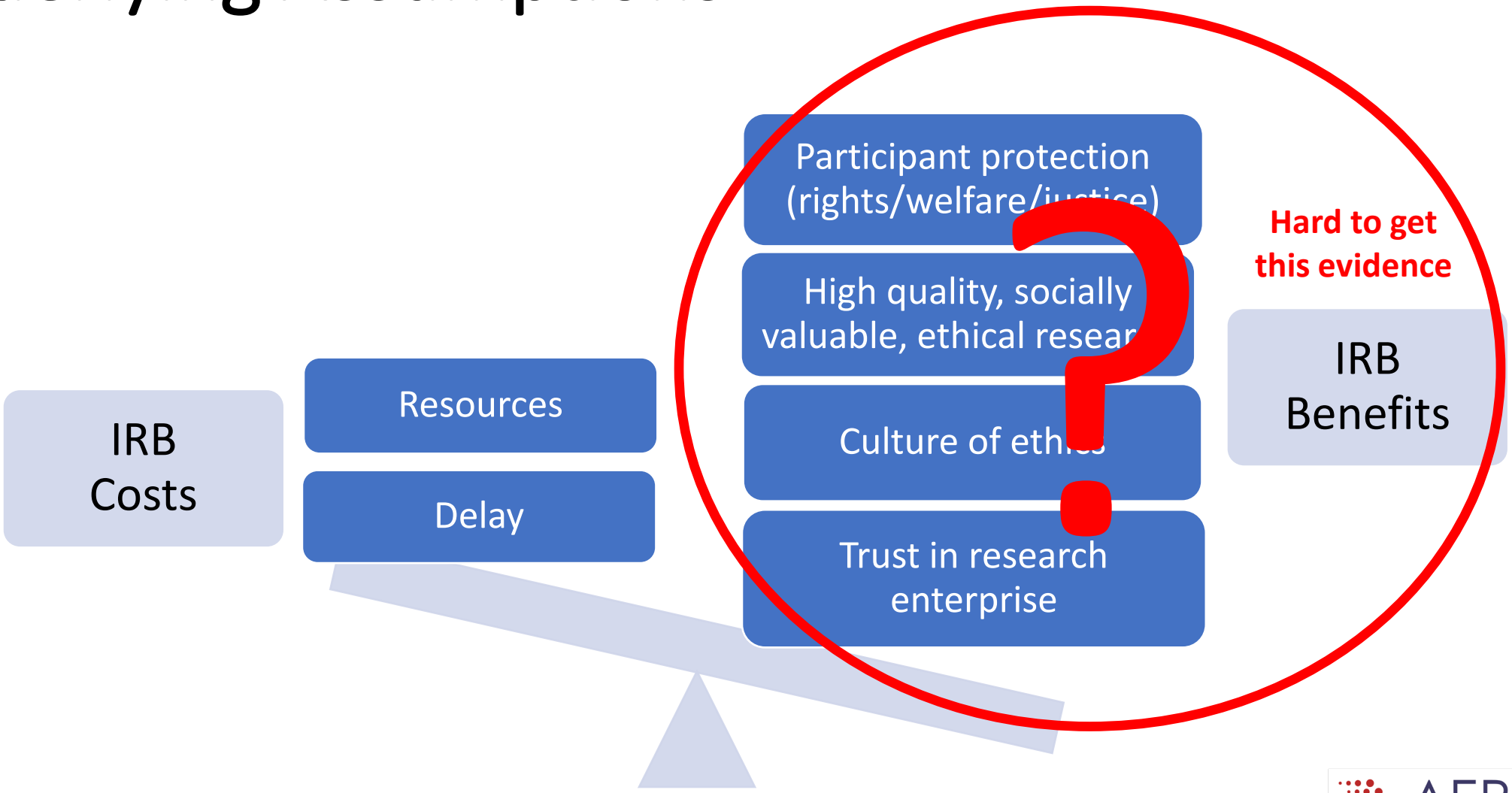


AEREO
Advancing Effective Research Ethics Oversight

Evidence of costs and burdens

- Inconsistency/variation between boards, esp re: risk/benefit analysis
- Inefficiency and redundancy – move to sIRB review + related problems
- Bureaucratic tinkering
- Expertise – cannot be expert in all types of research, may demand changes that weaken science
- Failure to justify decisions
- Record review, not “on-the-ground” oversight

Underlying Assumptions

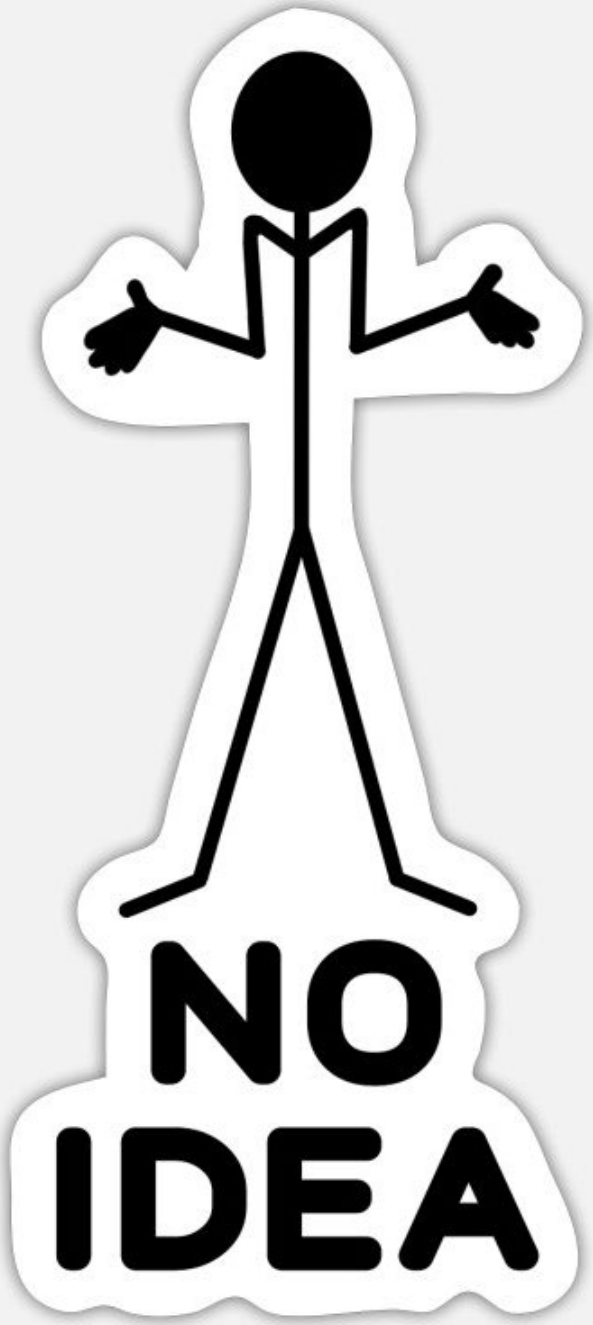


AEREO
Advancing Effective Research Ethics Oversight

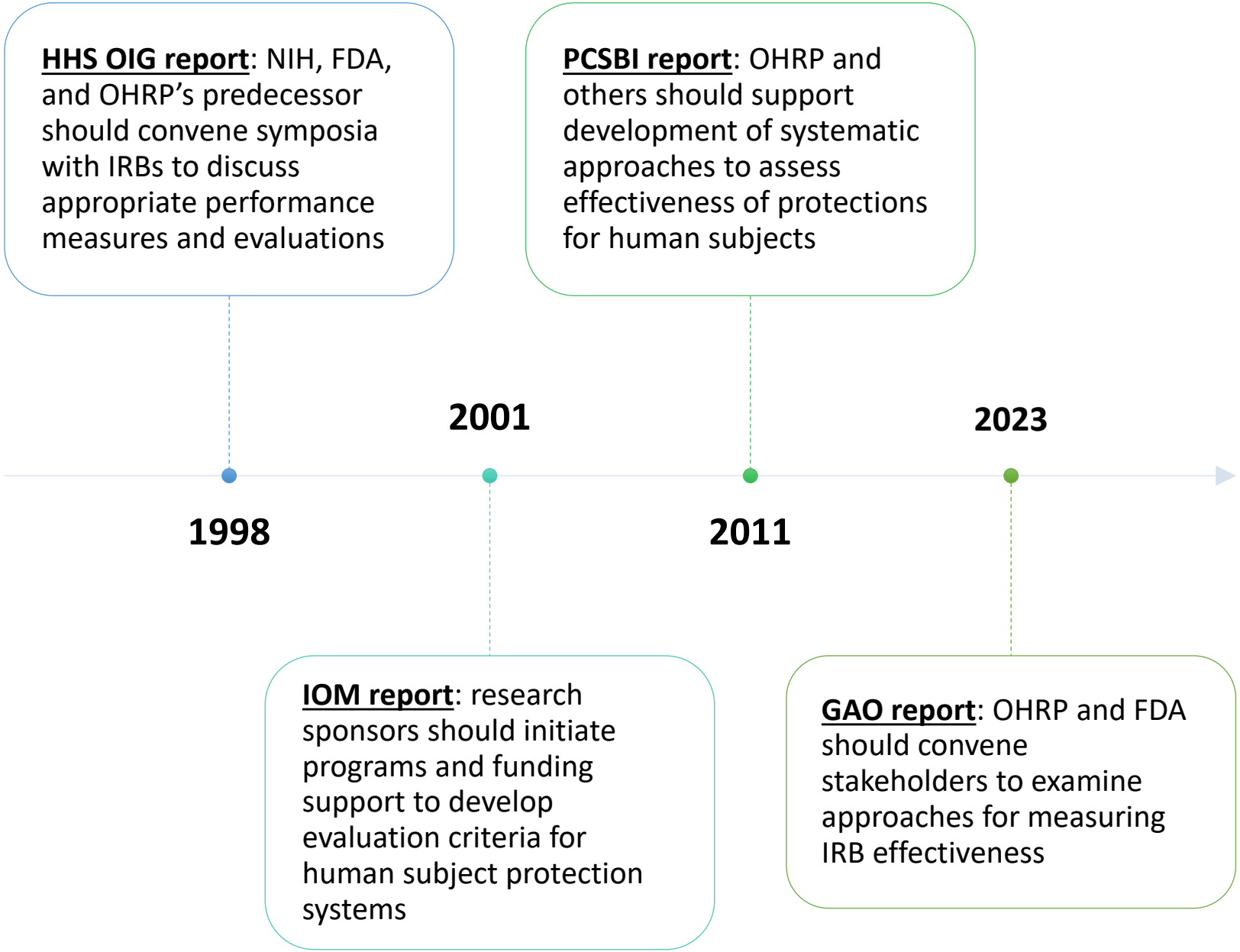
What's the result?

- Hard to know whether IRBs/HRPPs are effective
  - Individually
  - Collectively
- Hard to compare them to each other
  - Within categories
  - Across categories (e.g., commercial v. university)
- Hard to make appropriate adjustments

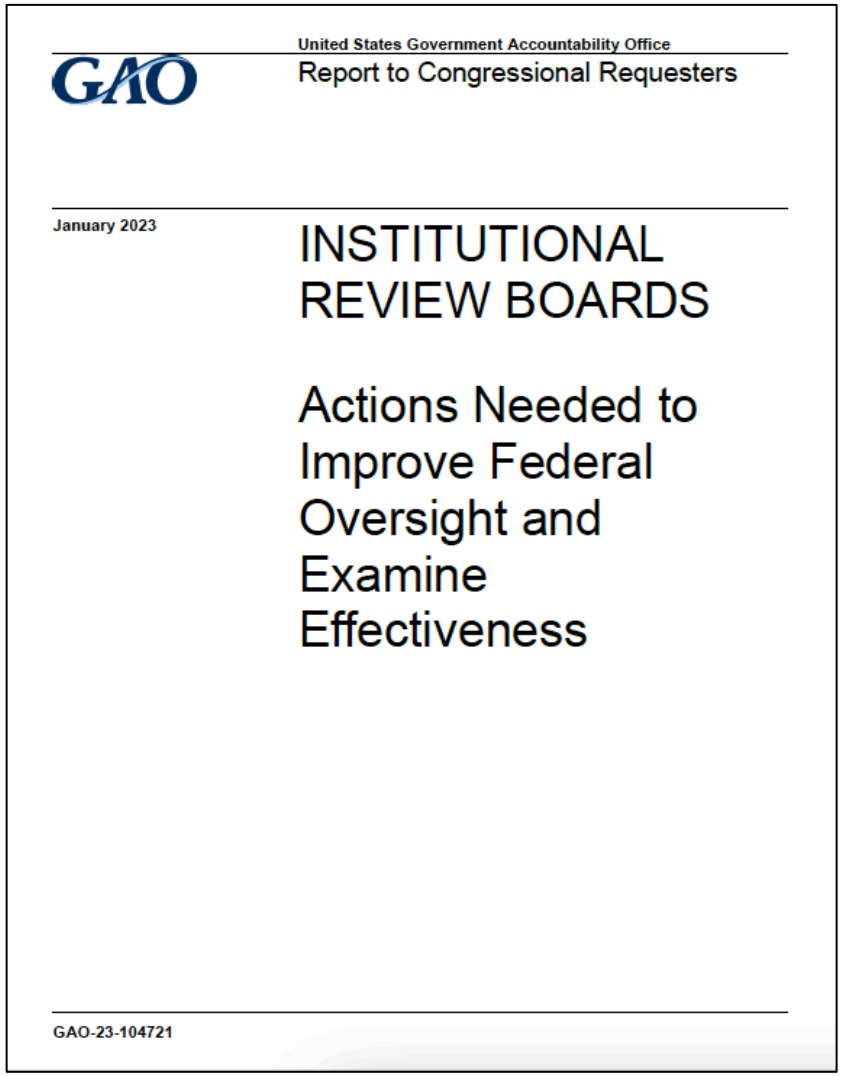
- Just left with a lot of complaints…



Calls to action…again and again



"OHRP and FDA have not assessed to what extent IRB reviews are effective in protecting human subjects. This is because the agencies have not determined the best approaches for doing so. Evaluating effectiveness is challenging in part due to the absence of validated measures and because IRBs are only one part of the framework of stakeholders responsible for protecting human subjects."


United States Government Accountability Office

GAO

Report to Congressional Requesters

January 2023

INSTITUTIONAL REVIEW BOARDS

Actions Needed to Improve Federal Oversight and Examine Effectiveness

GAO-23-104721

Without better measures, the focus has been on regulatory compliance, researcher satisfaction, and efficiency.

AJOB EMPIRICAL BIOETHICS
https://doi.org/10.1080/23294515.2022.2090641

How Do Accredited Organizations Evaluate the Quality and Effectiveness of Their Human Research Protection Programs?

Holly Fernandez Lynch[a] and Holly A. Taylor[b]

[a]Department of Medical Ethics & Health Policy, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [b]Department of Bioethics, Clinical Center, National Institutes of Health, Bethesda, Maryland, USA

Approaches to QEE

- Current measures
  - Turnaround time
  - Compliance
  - Feedback from/about IRB members
  - Researcher satisfaction
  - Uncommon: participant perspectives/experience
- Practical definitions
  - Quality = compliance, operational quality (not review quality)
  - Efficiency = turnaround time
  - Effectiveness = relationship-building with investigators, researcher perception of HRPP/IRB (NOT participant protection)

Social Science & Medicine 292 (2022) 114614

Contents lists available at ScienceDirect

Social Science & Medicine

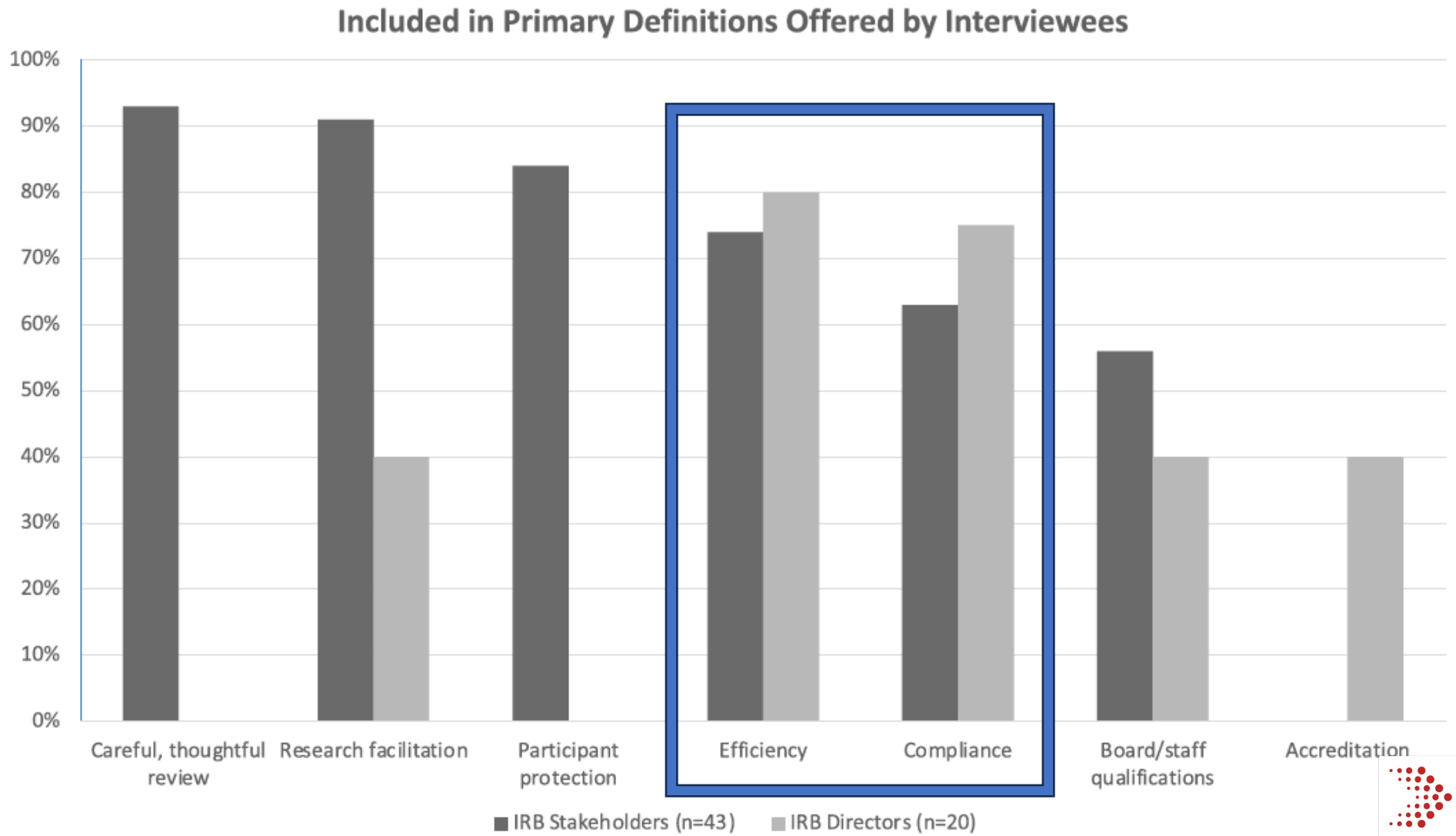
journal homepage: www.elsevier.com/locate/socscimed

"We measure what we can measure": Struggles in defining and evaluating institutional review board quality

Holly Fernandez Lynch *, Whitney Eriksen, Justin T. Clapp

Perelman School of Medicine, University of Pennsylvania, USA

Results: Essential elements of IRB quality



AEREO
Advancing Effective Research Ethics Oversight

IRBs were NOT created just to focus on compliance and efficiency.

The Problem(s)

- Compliance and efficiency are necessary but not sufficient
- Easy to measure but problematic
  - Regs relate to subject protection but are not comprehensive
  - Room for lots of variation w/i the regs – so what's quality?
  - How can we understand efficiency if we don't understand quality?

The Problem(s)

- "Audit culture" – focus on metrics over substantive goals
  - Box checking, expanding bureaucratic requirements, rote application of rules w/o attention to reasons
  - Regulations over ethics
  - Detracts from quality, impedes research
  - Good example: CYA consent forms
- Conservativism
  - Better safe than sorry
  - More likely to get "dinged" for letting bad research go through than inhibiting good research
- Self-assertion

What to do? 2 current lines of thought…

Participant protection and ethical quality are too hard

Best we can do is evaluate IRBs based on their **structure and process** (e.g., resources, policies, procedures, compliance, etc.)

Structure and process measures are only **proxies** for what matters, we must evaluate **outcomes** (i.e., what IRBs achieve) – but no adequate outcome measures have been established yet

The Third Way: IRB Reasonableness

Proposal/hypothesis: The best way to evaluate IRBs is by asking if they are "reasonable"

Why? Because IRBs apply standards, not rules

Rules

Policymakers can be specific up front, want to minimize discretion

Bright lines, not case-specific, inflexible

No judgment needed

Ex. Speed limits, voting age

Standards

Policymakers can't be specific up front, want to rely on experts

Open-ended, balancing, consider circumstances

Require judgment

Ex. reasonable accommodation, reasonable care, probable cause

Research ethics relies on standards

Regulatory examples

- Risks “minimized” and “reasonable”
- Subjects not “unnecessarily” exposed to risk
- Subject selection “equitable”
- Consent “informed”
- Other examples
  - Minimal risk
  - Practicability

45 CFR 46

Ethical requirements

- Social “value”
- Scientific validity
- “Fair” subject selection
- “Favorable” risk-benefit ratio
- Independent review
- Informed consent
- Respect for subjects

Emanuel, Wendler, Grady, 2000

AEREO
Advancing Effective Research Ethics Oversight

Research ethics relies on standards

Regulatory examples

- Risks “minimized” and “reasonable”
- Subjects not “unnecessarily” exposed to risk
- Subj
- Con
- Oth
  - M
  - R

45 CFR 46

If we could be more specific, we’d adopt rules (and maybe we wouldn’t need IRBs at all)

Ethical requirements

- Social “value”
- Scientific validity
- lection
- benefit
- iew
- lt
- Respect for subjects

Emanuel, Wendler, Grady, 2000

AEREO
Advancing Effective Research Ethics Oversight

IRBs interpret standards

- It's often not helpful to ask if an IRB got it "right" because standards have several acceptable answers
- Instead, more appropriate to ask if the answer/approach is reasonable
  - Reasonableness is the outcome of interest
- This is a prevalent approach in law!
  - E.g., medical malpractice
  - Evaluating quality of judges and juries

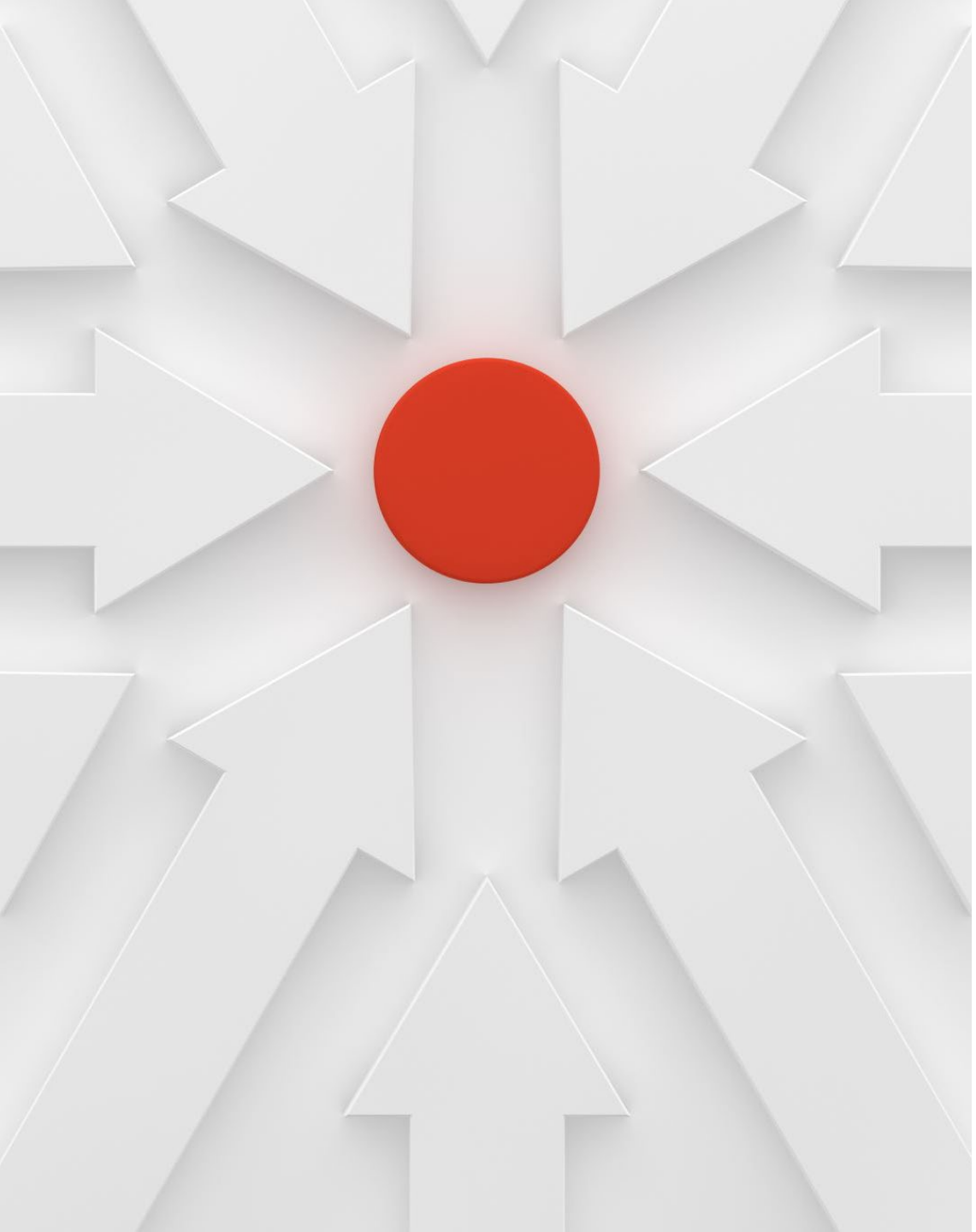
- IRBs are meant to offer **procedural protection**
  - Group of independent experts and stakeholders evaluate the acceptability of proposed research, with participant rights/welfare in mind
  - A promise of ethical acceptability – not avoidance of harm

AEREO
Advancing Effective Research Ethics Oversight

What about other IRB outcomes?

Outcomes raising ethical concern could mean:

1. Something out of IRB's control/purview
2. IRB's determination was unreasonable (out of bounds)
3. Disagreement about what is reasonable (which is why we have standards, not rules) → need further deliberation to clarify what is truly reasonable



The work, then, is to **identify the elements of IRB Reasonableness that can indicate their quality**, thereby allowing decisions to be defended as reasonable - and as achieving reasonable outcomes - even if they cannot be confirmed as "right."

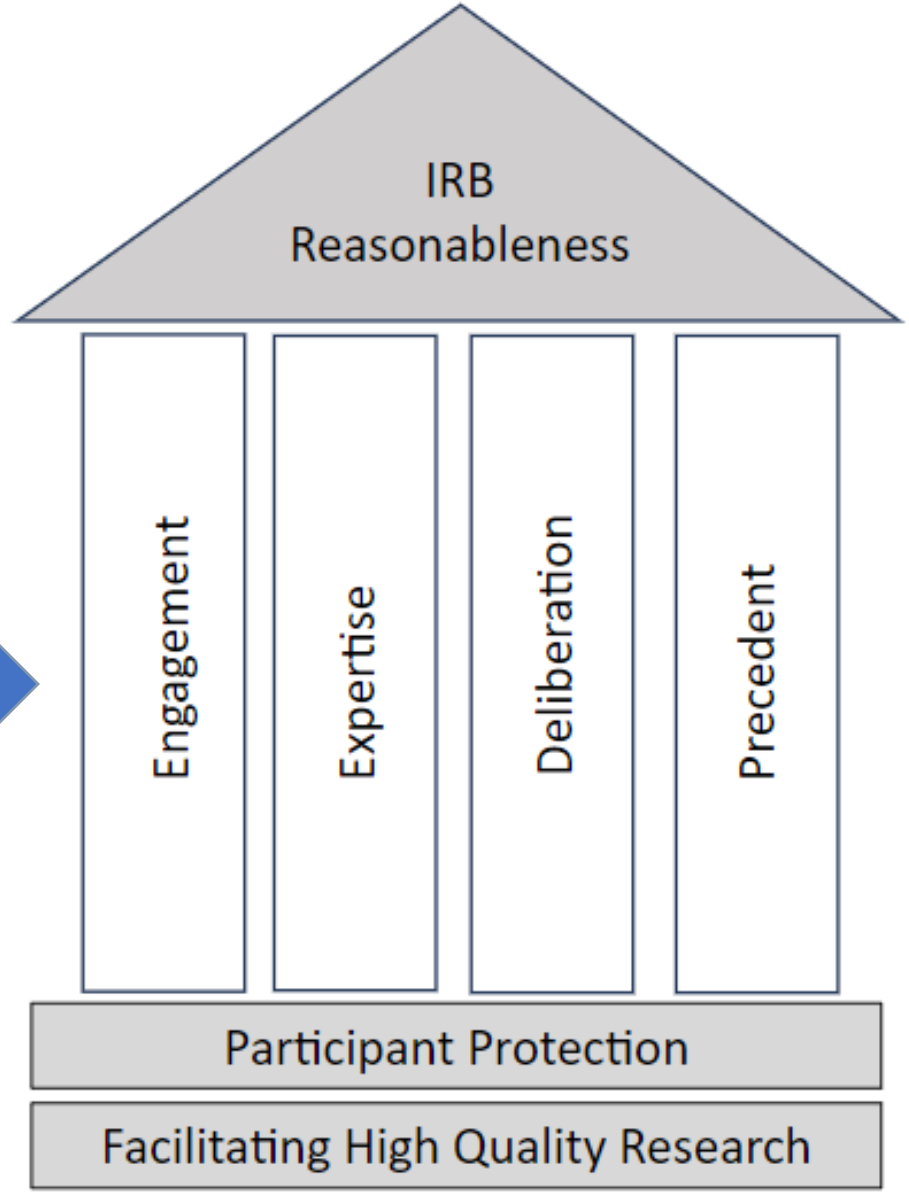
AEREO

Advancing Effective Research Ethics Oversight

www.aereo.org

Pillars of IRB Quality (PIQs)

Pillars of IRB Quality



Regulatory compliance and efficiency

ENGAGEMENT

A reasonable IRB…

Must be aware of the perspectives of and responsive to input from those affected by their decisions, including **research participants** and their communities, as well as the **investigators** whose work IRBs oversee, establishing a culture of trust, respect, accountability, and open communication with these IRB “constituents”

EXPERTISE

A reasonable IRB…

Provides proficient, objective review of research activities under its purview, through expert members, staff, and consultants

DELIBERATION

A reasonable IRB…

Carefully deliberates about challenging ethical issues in a way that blends various types of expertise and perspectives to achieve conclusions that are stronger and better justified than would be possible for any individual reviewer acting alone

PRECEDENT

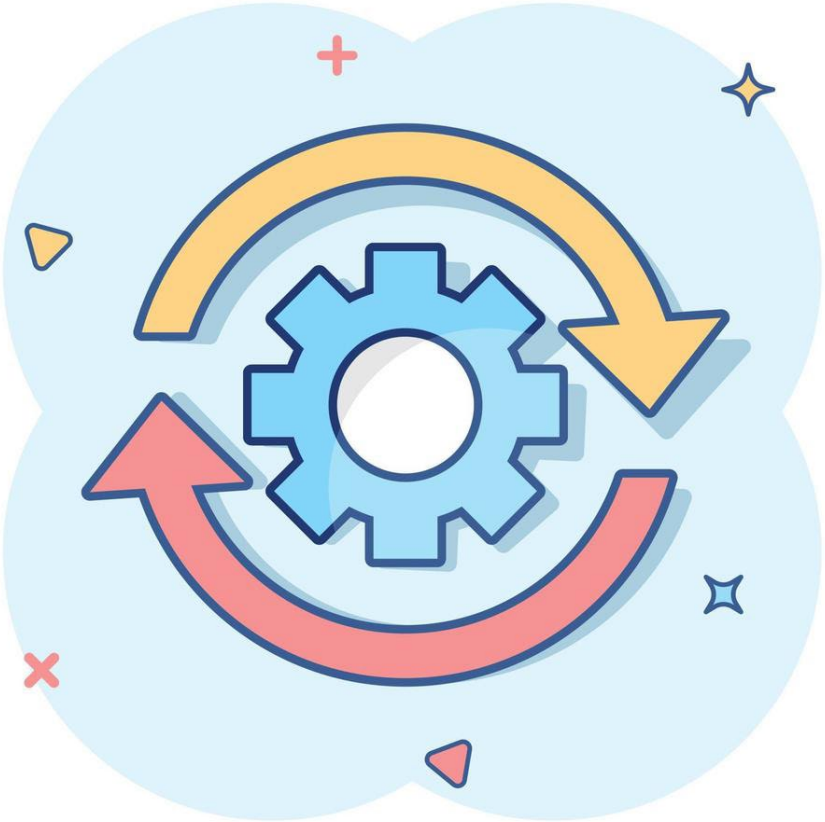
A reasonable IRB…

Must learn from and build on prior decisions to give meaning to ethical standards through iterative analysis of fact-specific cases, avoid inconsistency, and support efficiency and predictability

And other pillars of quality…

Proposal: PIQs and Reasonableness

- The Pillars of IRB Quality establish the elements of IRB reasonableness
- Focus on PIQ Performance
  - Defining PIQ parameters
  - Developing PIQ performance assessments
  - Generating PIQ resources and interventions
  - Identifying additional PIQs
- Cultivate a Learning IRB System



The Learning IRB System

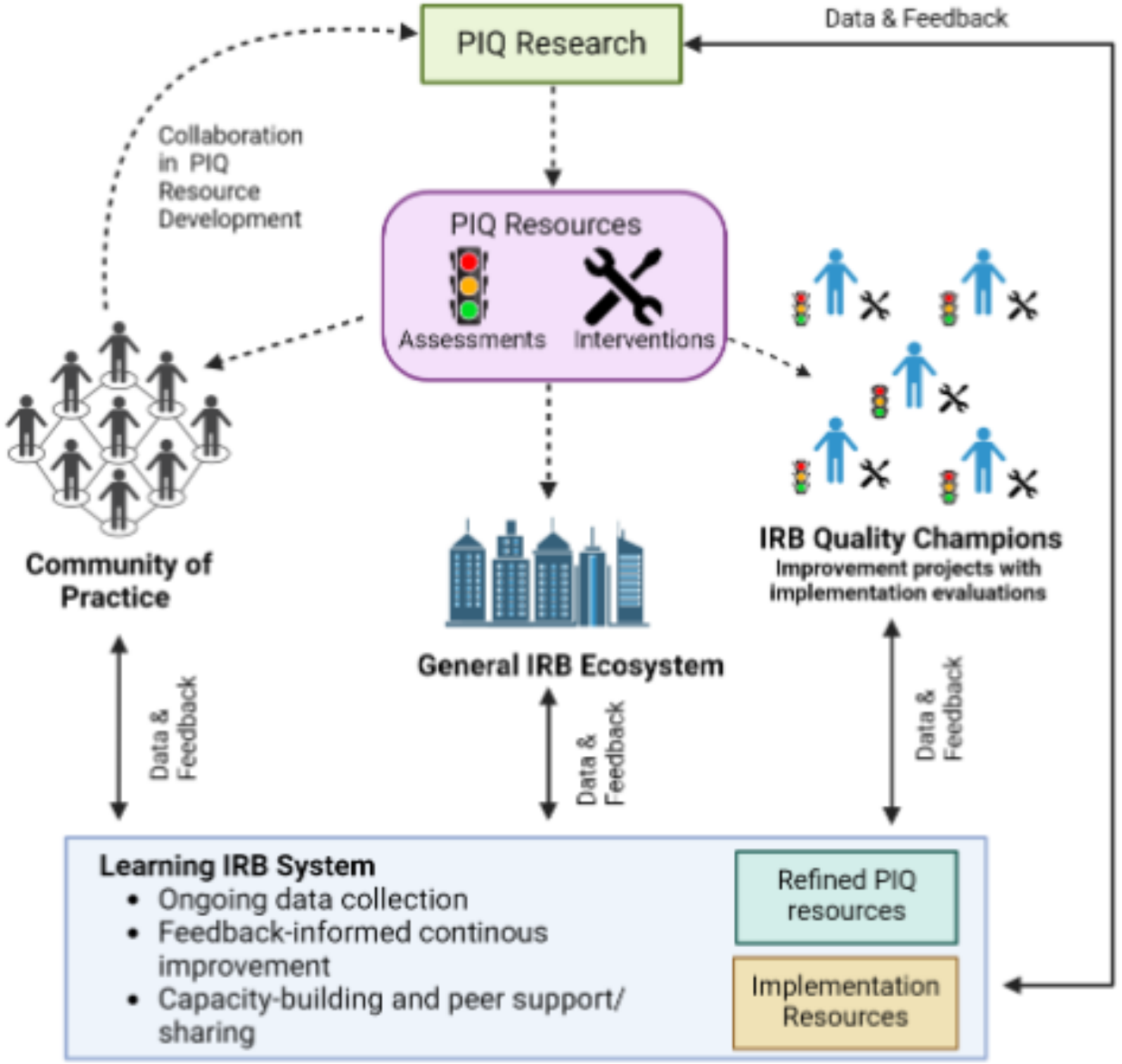


Figure 3: The Learning IRB System, created with BioRender

Key Takeaways for Researchers

- Attend to compliance but call out IRB audit culture – ask why, seek reasons
- Emphasize ethical goals when seeking solutions
- Partner with your IRB to improve culture
- Take your responsibility for participant protection seriously

- IRBs can be a barrier – but this should be a team effort to facilitate ethical research

Thank you!

Ask me anything about…IRBs, standard of care research, paying participants, compassionate use

lynchhf@pennmedicine.upenn.edu

www.aereo.org

AEREO

Advancing Effective Research Ethics Oversight